Spironolactone-Induced Unilateral Gynecomastia

Sahana Hadihalli Veeregowda, Jayakumar Jyothinagaram Krishnamurthy, Bhuvana Krishnaswamy, Sarala Narayana

Department of Pharmacology, Sri Devaraj Urs Medical College, Sri Devaraj Urs Academy of Higher Education and Research, Kolar, Karnataka, India

Abstract

Gynecomastia is benign enlargement of male breast, drug-induced gynecomastia accounts for about 25%. We are reporting a case of spironolactone-induced unilateral gynecomastia. A 52-year-old male patient receiving multiple antihypertensives including hydrochlorothiazide presented with muscle weakness and easy fatigability. Investigations revealed hypokalemia; he was advised to stop hydrochlorothiazide and consume potassium-rich diet; since he did not respond to this, spironolactone was added. The patient improved symptomatically but developed painful swelling of the right breast after 12 months of treatment which was suspected to be spironolactone-induced gynecomastia. Within a month of stopping the drug, pain in the right breast subsided followed by decrease in size of swelling. Literature search indicates bilateral gynecomastia by spironolactone, but when clinician encounters unilateral presentation, they should consider the possibility of drug-induced etiology. Patients should be educated about this while prescribing, and eplerenone can be a safe alternative.

Keywords: *Drug induced, eplerenone, spironolactone, unilateral gynecomastia*

Introduction

Gynecomastia is clinically defined as benign enlargement of male breast due to proliferation of glandular component with deposition of fat.[1] It is derived from Greek words "gynae" meaning woman and "mastos" which means breast. This clinical condition can occur at all ages and involve one or both breasts.[2] Normally, estrogen stimulates the proliferation of breast epithelial cells, and androgens have an inhibitory effect. Gynecomastia usually results due to imbalance between actions of estrogen and androgen on the breast tissue. The causes for gynecomastia can be either physiological (neonatal, pubertal, or involutional) or pathological conditions (drug induced, endocrine disorders such as testicular, adrenocortical, or pituitary tumors, hyperthyroidism, and nonendocrine causes such as cirrhosis, starvation, stress, and renal failure).[1-3]

Drug-induced gynecomastia accounts for about 20%–25% of all new cases in adults. Drugs associated with gynecomastia are bicalutamide, flutamide, nilutamide, leuprolide, goserelin, metronidazole, ketoconazole, isoniazid, minocycline, digoxin, spironolactone, amlodipine, nifedipine, verapamil, captopril, enalapril, amiodarone, methyldopa, minoxidil, methotrexate, vincristine, diazepam, phenytoin, androgens, anabolic steroids, estrogen, theophylline, D-penicillamine, cimetidine, and metoclopramide.[1,2] Spironolactone, which is a potassium-sparing diuretic, has antiandrogen action and causes bilateral gynecomastia, but we report a case of unilateral gynecomastia.

Case Report

A 52-year-old male, nonsmoker and nonalcoholic, was on amlodipine, atenolol, and hydrochlorothiazide for control of hypertension. After a year of taking the above medications, he presented to his physician with muscle weakness and easy fatigability. On examination, his vital parameters including blood pressure were normal, but serum potassium was low. This was attributed to tablet hydrochlorothiazide and it was discontinued; he was advised to consume diet rich in potassium and continue the other antihypertensives. In spite of this, the patient's symptoms persisted and hence tablet spironolactone 25 mg once a day was added to the existing medications. After 12 months of treatment, muscle weakness and fatigability reduced but he developed painful swelling of the right breast [Figure 1]. On examination, tender mobile lump was palpable in the right breast. Fine-needle aspiration cytology

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Address for correspondence:
Dr. Sarala Narayana, Department of Pharmacology, Sri Devaraj Urs Medical College, Sri Devaraj Urs Academy of Higher Education and Research, Tamaka, Kolar - 563 101, Karnataka, India.
E-mail: n_sarala@rediffmail.com

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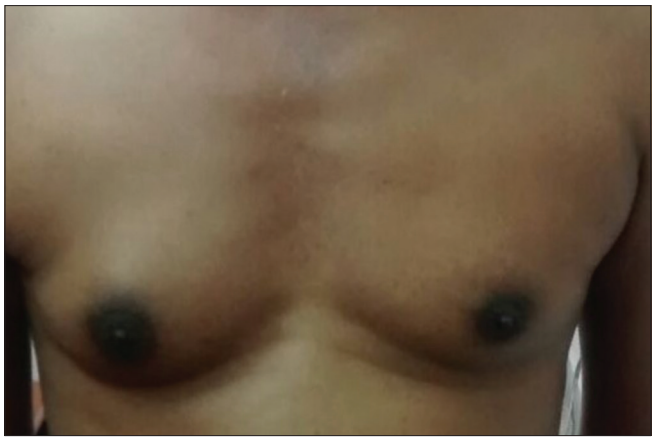

Figure 1: Comparison of the right breast with the left

of the right breast done was normal. It was suspected to be spironolactone-induced gynecomastia and the drug was withdrawn (dechallenge) while other regular medications were continued. On dechallenge, pain in the right breast subsided drastically within a month followed by decrease in the size of the swelling. After 3 months, swelling and pain in the right breast had reduced completely. Limitation: Exposing the patient to spironolactone again may lead to recurrence which is not ethical and hence rechallenge was not carried out.

Discussion

Gynecomastia was first described by Paulus Aegineta in 625–690 AD, and he had explained it to be due to the formation of fat.[3] Pain and swelling are the cardinal features of gynecomastia which are the effects of hormonal imbalance affecting the breast tissue. Spironolactone can cause gynecomastia by multiple mechanisms. It blocks the androgen receptors and prevents the binding of testosterone and dihydrotestosterone. It decreases testosterone production from testes by inhibiting enzymes 17α-hydroxylase and 17, 20-desmolase . In addition it displaces testosterone from sex hormone-binding globulin, and enhances the metabolic clearance of testosterone. It increases the levels of estrogen by enhancing peripheral conversion of testosterone to estradiol.[4-6] The antiandrogen action of spironolactone responsible for the development of gynecomastia depends on the dose and duration of treatment and is usually bilateral.[6-8] A study conducted by Rose *et al*. has reported that 6 out of 16 patients with hypertension treated with spironolactone developed gynecomastia. They also found low blood testosterone levels and higher estradiol levels among these patients compared to controls which confirms hormonal imbalance as the causative factor for spironolactone-induced gynecomastia.[9] Bowman *et al*. mention that there were 63 reports of spironolactone-induced gynecomastia as per US Food and Drug Administration Adverse Event Reporting System database.[10] Engbaek *et al*. reported 5.2% patients manifested with gynecomastia.[11] Deepinder and Braunstein *et al*. observed 10% of 1663 heart failure patients who received 25 mg/day of spironolactone for 24 months had developed gynecomastia.[12]

Differentiating true gynecomastia from lipomastia or pseudogynecomastia is difficult. The glandular tissue on palpation is a disc of firm tissue and is concentric with the nipple-areolar complex in case of true gynecomastia but tissue is not of the same texture in pseudogynecomastia. However, ultrasound of breast is recommended as first-line investigation, followed by mammography to confirm the diagnosis. In most of the patients, stopping the offending agent is sufficient, but in those with severe pain, psychological discomfort, and for cosmetic reasons, danazol, selective estrogen receptor modulator such as tamoxifen and aromatase inhibitor such as anastrozole are used.[2] Eplerenone, selective aldosterone antagonist, has greater selectivity for mineralocorticoid receptors compared to spironolactone.[13] It is about 370 times less potent in blocking dihydrotestosterone-activating androgen receptors and hence lesser incidence of gynecomastia. Surgery is indicated only in long-standing symptomatic cases and failure of medical management.

Conclusion

Spironolactone-causing bilateral gynecomastia is well established but unilateral presentations reported are few. Eliciting proper history and performing examination can result in correct diagnosis. Stopping the offending agent resolves the problem and thereby can save the patient from embarrassment, anxiety, physical discomfort of investigations, and surgical procedure. Patients should be informed about this side effect while prescribing this drug and alternatively eplerenone can be used.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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